Vision Recovery and Connectivity by Fetal Retinal Sheet Transplantation in an Immunodeficient Retinal Degenerate Rat Model.

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Authors: Magdalene J Seiler, Robert E Lin, Bryce T McLelland, Anuradha Mathur, Bin Lin, Jaclyn Sigman, Alexander T De Guzman, Leonard M Kitzes, Robert B Aramant, Biju B Thomas

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Public Summary:
Diseases affecting the light-sensing cells in the retina (photoreceptors) affect millions of people. Although there are several treatments in clinical trials to delay vision loss in early stages of retinal degeneration (RD), there are currently no treatment options available for more progressed stages. This study investigated retinal progenitor sheet transplants in a new rat model of RD with a defective immune system that do not reject foreign cells (RD nude rats). These rats received transplants at one month of age when they would turn blind. Rats expressing a specific marker in all of their cells (human placental alkaline phosphatase) were used to provide donor tissue for retinal progenitor sheet transplants. The eyes of transplanted rats were imaged in vivo using optical coherence tomography (OCT) which showed the placement and development of the transplants in the subretinal space over time. Different methods were used to test whether the transplants could improve visual function: tests of visual acuity (optokinetic testing how rats can discriminate moving black and white stripes), and electrical responses to light from the cornea (electroretinogram = ERG) and the brain (superior colliculus = SC). In optokinetic testing, rats with retinal sheet transplants had improved visual acuity compared to RD rats without transplants or with sham surgery. No ERG responses could be recorded from RD nude rats with or without transplants. On the other hand, transplanted rats exhibited robust responses in the superior colliculus to light (as tested up to 7.5 month after transplantation) whereas age-matched control RD nude rats had no responses. Responsive areas in the brain corresponded to the placement of the transplant in the host retina. The quality of visual responses correlated with transplant organization and placement. Analysis of the transplants showed development of photoreceptors and other retinal cells in layers, and integration with the host retina. In summary, this study provides proof of concept that retinal progenitor sheet transplants integrate into the RD recipients' retina and recover significant visual function.

Scientific Abstract:
Purpose: To characterize a recently developed model, the retinal degenerate immunodeficient S334ter line-3 rat (SD-Foxn1 Tg(S334ter)3Lav) (RD nude rat), and to test whether transplanted rat fetal retinal sheets can elicit lost responses to light. Methods: National Institutes of Health nude rats (SD-Foxn1 Tg) with normal retina were compared to RD nude rats with and without transplant for morphology and visual function. Retinal sheets from transgenic rats expressing human placental alkaline phosphatase (hPAP) were transplanted into the subretinal space of RD nude rats between postnatal day (P) 26 and P38. Transplant morphology was examined in vivo using optical coherence tomography (OCT). Visual function was assessed by optokinetic (OKN) testing, electroretinogram (ERG), and superior colliculus (SC) electrophysiology. Cryostat sections were analyzed for various retinal/synaptic markers and for the expression of donor hPAP. Results: Optical coherence tomography scans showed the placement and laminar development of retinal sheet transplants in the subretinal space. Optokinetic testing demonstrated a deficit in visual acuity in RD nude rats that was improved after retinal sheet transplantation. No ERG responses were detected in the RD nude rats with or without transplantation. Superior colliculus responses were absent in age-matched control and sham surgery RD nude rats; however, robust light-evoked responses were observed in a specific location in the SC of transplanted RD nude rats. Responsive regions corresponded to the area of transplant placement in the eye. The quality of visual responses correlated with transplant organization and placement. Conclusions: The data suggest that retinal sheet transplants integrate into the host retina of RD nude rats and recover significant visual function.